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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,303	03/29/2007	Masayori Inouye	601-1-131PCTUS	9634

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EXAMINER	
HIBBERT, CATHERINE S	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,303	INOUYE ET AL.	
	Examiner	Art Unit	
	CATHERINE HIBBERT	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,27-31 and 36-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,27-31 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The finality of the previous action is withdrawn in view of the new grounds of rejection presented in this action. This US Application 10/560,303 filed 12 December 2005, which is a national stage entry of PCT/US04/18571, filed 14 June 2004, claims benefit of US Provisional Applications 60/478,515 filed 6/13/2003 and 60/543,693 filed 2/11/2004. Applicant's Amendment to the Claims filed 19 April 2011 is received and entered. Claims 1-23, 25-26, 32-35 are cancelled. Claims 36-38 are new. Claims are 24, 27-31 and 36-38 are pending and under examination.

Priority

Claims 24, 27-31 and 36-38 receive priority to 14 June 2004, the filing date of the priority document PCT/US04/18571. The base claims 24, 31 and 36 each recite the limitation "wherein amino acid sequences of said polypeptide encoded by said mutated nucleic acid sequence *are not altered* by said mutating", but support for the limitation "are not altered" cannot be found in the US Provisional Applications 60/478,515 filed 6/13/2003 and 60/543,693 filed 2/11/2004 but can be found in the PCT/US04/18571 document. Additionally, support for the sequence of SEQ ID NO: 4, pertaining to claims 28, 31, 36, 37 and 38 cannot be found in the US Provisional Application 60/478,515 filed 6/13/2003 but is found in 60/543,693 filed 2/11/2004.

Response to Amendments

The objection to cancelled claims 25, 26, and 32 is moot.

The objection to claim 27 and 28 is withdrawn.

The rejection of claims 24 and 29-31 under 35 U.S.C. 112, first paragraph, is withdrawn in view of claim amendments.

Claim Rejections - 35 USC § 112-new grounds of rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24, 27-31 and 36-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a polypeptide using the cell strains, substrates and growth conditions as shown in the instant

specification under Example VI, does not reasonably provide enablement for a method of making a polypeptide using any cell types and under any growth conditions as now claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following: 1) *The nature of the invention.* The invention involves producing polypeptides in any type of cell under any growth conditions based on the cleavage specificity of MazF and PemK endoribonucleases, the MazF and PemK comprising the sequences of SEQ ID NO: 2 and 4, respectively, which reads on the wild-type *E. coli* MazF and PemK endoribonucleases, respectively. Specifically, the instantly claimed invention requires that the MazF recognizes the ACA sequence for cleavage and the PemK recognizes the UAX sequence (where X is a C, A, or U) for cleavage. In addition, the invention requires that a complex balance is achieved between total inhibition of protein in a cell while still producing the desired protein of interest in the cell.

2) *The breadth of the claims.* The claimed invention is broad in scope regarding any cells types, and any growth and/or undefined reaction conditions. Regarding claim 31, it reads on both cell-free systems such as shown in Examples I and VI in the instant specification as well as on *in vivo* methods.

3) *The state of the art.* The closest art to the instantly claimed invention is found in the reference of Christensen et al and the two references of the inventors work shown in Zhang et al (2003) and Zhang et al (2004):

Christensen et al, "Toxin-antitoxin Loci as Stress-response-elements: ChpAk/MazF and ChpBK Cleave Translated RNAs and are Counteracted by tmRNA" (Journal of Molecular Biology, 2003, Vol 332, pages 809-819),

Zhang et al, "MazF Cleaves Cellular mRNAs Specifically at ACA to Block Protein Synthesis in Escherichia coli" (Molecular Cell, Vol 12, pages 913-923, October 2003),

Zhang et al "Interference of mRNA Function by Sequence-specific Endoribonuclease PemK" (The Journal of Biological Chemistry, Vol 279, No. 20, pages 20678-20684, March 15, 2004).

Christensen et al teach that the mRNA interferase MazF from *E. coli* (also called ChpAK) inhibits translation by cleavage of specific codon recognition sequences in mRNA coding regions (e.g., abstract and Figure 1 and legend). Christensen et al disclose transfecting an *E. coli* cell with plasmid nucleic acids encoding the mRNA interferase MazF/chpAK (e.g., page 811, lines 1-4 and bottom right paragraph). Christensen et al disclose overexpressing the sequence encoding the MazF in the cell together with an *lpp* mRNA (i.e., a control polypeptide of interest) in order to measure the effect of the MazF on the inhibition of the translation of the *lpp* mRNA into the control polypeptide of interest. Christensen et al disclose that *in vivo* experiments resulted in codon-dependent

cleavage of the *lpp* mRNA cleavage performed by wild-type MazF/ChpAK from *E. coli* (which inherently comprises SEQ ID NO:2). Regarding claim 30, Christensen et al teach incubating cells prior to or during protein expression in a cell in media having a radioactively labeled isotope in order to measure the amount of protein synthesis (page 818, left column, paragraph headed: "Rates of translation and replication). However, instead of the ACA recognition sequence recited in the instantly claimed invention, Christensen et al report that the MazF/ChpAK cleaved between the second and third bases of a GGU codon and an AAA codon (page 812, top right paragraph) and cleaved the tmRNA at the UAA stop codon and at additional sense codons (page 812, second right paragraph).

The Zhang et al references are the instant inventors' work (although having different inventive entities) and disclose that the mRNA recognition site for the MazF mRNA interferase is specifically the ACA site.

These three state of the art references teach methods of measuring the effect of mRNA interferases, MazF and PemK, on protein synthesis but do not contemplate using the MazF and PemK cleavage specificity to alter the mRNA sequence encoding a desired polypeptide in combination with expression of the MazF or PemK to inhibit total cellular protein synthesis in order to produce a polypeptide of interest. The Christensen et al reference shows the art in this area of research is unpredictable because this reference shows the MazF has a different cleavage recognition sequence under their experimental conditions in comparison to the Zhang et al references. In addition, the Christensen et al reference shows that the MazF activity in the cell is different depending on the nutritional

stress (i.e., growth conditions) of the cells (e.g., abstract). Thus, the nature of the instantly claimed invention must be considered experimental and unpredictable.

4) *The level of predictability in the art.* The art in the area of the instantly claimed invention is unpredictable because both Christensen et al and Munoz-Gomez et al, in "Insights into the specificity of RNA cleavage by the *Escherichia coli* MazF toxin", FEBS Letters, No. 567, pp. 316-320, 2004) report that the ChpAk/MazF endoribonuclease from *E. coli*, cleaves mRNA in the cell at a site that is different from the claimed ACA site. Christensen et al report that the MazF/ChpAK cleaved between the second and third bases of a GGU codon and an AAA codon (page 812, top right paragraph) and cleaved the tmRNA at the UAA stop codon and at additional sense codons (page 812, second right paragraph). Therefore, these references show that the research required for one of ordinary skill in the art to be able to make and use the instantly claimed invention in any cells or under any cell-free reaction conditions would be an endeavor which requires extensive inventive research.

5)/6) *Guidance provided in the Specification and Working examples*: The applicant's claimed invention of a method of making a polypeptide (i.e., claim 31) or making a polypeptide in a cell (i.e., claims 24 and 36) is disclosed in Example VI in the instant specification. The Applicants disclose in the instant specification that the results shown in Example I, first using purified MazF protein in prokaryotic and eukaryotic cell-free translation systems and then using *in vivo* experiments in *E. coli* BW25113 cells transfected with pBAD-MazF (i.e., a nucleic acid encoding MazF comprising SEQ ID NO:2), indicate that MazF functions as a highly sequence-specific endoribonuclease,

which cleaves cellular mRNAs at ACA sites and thus blocks whole protein synthesis in the cell (e.g., see page 82, paragraph 0284 and Figure 2E and legend). In addition, regarding PemK, the Applicants disclose in Example IV (page 98), that purified PemK inhibits protein synthesis in an *E. coli* cell-free system and that PemK cleaves single-stranded RNA preferentially at the 5' or 3' side of the "A" nucleotide in "UAX" sequences, where X is C, A or U. Also, *in vivo* results shown in Example IV indicate that upon the *in vivo* induction of PemK in *E. coli* BW25113 cells transfected with the pBAD-K (i.e., a nucleic acid encoding PemK comprising SEQ ID NO:4) the PemK cleaves cellular mRNAs to block protein synthesis (e.g., see Example IV, page 98). However, the applicants show no *in vivo* examples using any other strains of E. coli or using any other prokaryotic cells or using any eukaryotic cells. In addition, the Applicants disclose on page 112 of the instant specification that PemK activity may cause total inhibition of protein a cell. Therefore, Applicants have not provided working examples or guidance on how to make or use the instantly claimed invention for the broadly claimed genus of any cell, especially in view of the apparent unpredictability of mRNA interferases in recognizing specific recognition sequences as shown for the MazF endoribonuclease recognition sequences under various nutritional stress (i.e., minimal media versus rich medium) and under different experimental conditions as discussed above regarding the Christensen et al and Munoz-Gomez et al references.

7) *The level of skill in the art.* The level of skill in the art is highly advanced, being that of a person holding a Ph.D or an M.D.; however, given the complex, unpredictable aspects of the invention, the broad scope of the invention, the lack of guidance presented

by applicants regarding the broad scope and the lack of working examples regarding the broad scope it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the invention as instantly claimed.

8) *The quantity of experimentation needed to make and/or use the invention.* Given the analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have practiced essentially trial and error experimentation in order to try to practice the claimed invention. Said experimentation must be considered to be undue and excessive.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Catherine Hibbert
Examiner AU1636

/NANCY VOGEL/
Primary Examiner, Art Unit 1636